1443 IMMUNOEDITING DRIVES MYC RELATED METABOLIC REPROGRAMMING FOR CANCER IMMUNE EVASION THROUGH NON-CANONICAL IFNγ-STAT3 PATHWAY

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Background Metabolic reprogramming in tumors, a recognized hallmark of cancer, has been found to contribute to the suppression of host anti-tumor immunity. The major drivers of metabolic reprogramming in tumors are thought to be oncogenic mutations and hypoxia. However, the reasons why metabolic switches are necessary in response to various environmental cues and the selective pressure exerted by the host's anti-tumor immunity remain unanswered. Therefore, we hypothesis that metabolic preference and reprogramming observed in tumor cells can be sculpted as a result of immunosurveillance.

Methods In our study, we utilize an immunodeficient genetic background or employ antibody-based cell depletion in the spontaneous tumor genetic mouse model. By applying comprehensive multi-omics analyses encompassing metabolomes, genomes, transcriptomes, and epigenomes, we aim to explore the metabolic evolution guided by immunosurveillance. Additionally, we also perform CRISPR screening by targeting metabolic-related enzymes to identify potential vulnerabilities that can enhance T cell anti-tumor responses.

Results Here, we report that T cell-mediated immunosurveillance during tumorigenesis instructs cMYC upregulation and metabolic reprogramming in tumor cells. This tumor-immune crosstalk is regulated by non-canonical interferon gamma-STAT3 signaling, which can further contribute to tumor immune evasion. Notably, our results also indicate that the immunosurveillance-driven metabolic reprogramming is controlled by transcriptomic and epigenomic changes, rather than genomic variations. Moreover, through our CRISPR screening, we also uncover potential metabolic targets which can rejuvenate T cell anti-tumor responses.

Conclusions Our findings reveal 'immunometabolic editing', which is governed by the previously unexplored role of interferon gamma in T cell-mediated immunosurveillance. We demonstrate that immunoediting influences the epigenetic architecture and gene expression in tumor cells, specifically emphasizing the cMYC-dependent metabolic reprogramming process. And a better understanding of the tug-to-war between the immune system and tumor metabolism will provide potential avenues for therapeutic interventions aimed at disrupting tumor immune evasion.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.1443